Neurobehavioral Effects of Lead

A Summary Review of Cross-Sectional and Longitudinal Studies

by

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There is a general concensus that high levels of lead exposure, in utero and during early childhood, can often lead to serious, even fatal sequelae. There is increasingly less concensus regarding the character and/or existence of neurobehavioral effects as one examines the literature pertaining to progressively lower levels of lead exposure. This is the case because we are moving down on the dose-response scale from the realm of a pure main lead effect toward a region in the dose-response scale where lead's effects are less discernable relative to other factors which influence child development, behavior and performance. In fact it is possible that "lead effects" at low exposure levels occur only as a result of interaction with other insults.

For the purpose of this review the history of neurobehavioral:lead research has been divided into several phases

Pre-1979: Cross-sectional, Retrospective Studies

Studies during this era, although often state-of-the-art at the time they were undertaken, are crude by today's standards. This literature has been subjected to frequent and thorough review (cf Bornschein et al., 1980; Lawther Report, 1980). Clearcut interpretation of the findings from these studies are hampered by their numerous methodological flaws. For example, lead exposure histories were poorly documented. Frequently, only a single recent blood lead value at the time of behavioral testing, was used, leading to poor separation between high lead exposure and low lead exposure groups. Other unreliable indices of lead exposure history have also been used, e.g. hair lead concentration.

Often no rationale was given for the selection of neurobehavioral tests used to index lead's posited effect on behavior or cognition. This resulted in too

many tests being administered, with an increased likelihood of incurring a false-positive finding. The use of insensitive tests increased the chance of false-negatives findings, while the use of non-standardized and/or subjective tests led to difficulties interpreting the studies findings.

Although these studies did little to resolve the question of whether or not lead causes neurobehavioral deficits at low levels, they did result in a heighted awareness of a potentially serious health hazard and the need for well designed and executed epidemiological studies of the etiology of poor neurobehavioral outcomes in school age populations.

1979-1983: Retrospective Studies

The first of a new generation of studies, which attempted to avoid the problems of the earlier studies, was that of Needleman et al., 1979. This study as well as those of five other research groups have been critically reviewed (Air Quality Criteria Document, 1984; Smith, 1985; Yule and Rutter, 1985; Harvey et al., 1984). Key aspects of these studies are summarized in Table 1 taken from Smith (1985). The results of the psychometric findings are summarized in Figure 1. The mean full scale I.Q. difference between the high and low lead exposure groups, as well as the 90% confidence interval for the estimate of the mean difference, is shown for each of the major reported studies. If the 90% confidence interval does not include zero (e.g., Needleman et al., 1979; Yule et al., 1981), then this is interpretated as the graphic equivalent of detecting a significant effect at $p<.05$. Two studies (Smith et al., 1983; Winneke et al., 1983) found mean differences of about 5 I.Q. points prior to adjustment for covariates and confounders. However after statistical adjustment, these differences were reduced to about 2.5 I.Q. points and were no longer

statistically significant. Much has been made of the fact that even though the majority of these studies have not found statistically significant lead effects, the effects are all in the hypothetized direction, i.e. high lead exposure groups performed more poorly than the low lead exposure groups (EPA, 1984). There is general agreement that before controlling for social factors there is an association between higher exposure levels and poorer performance on psychometric tests. It is also generally agreed that after statistical adjustment the size of the group effect is reduced to an average of about 2.5 I.Q. points for the studies in question. However, there is considerable controversy about the appropriateness of the statistical adjustment and the interpretation of why it results in a reduction in the size of the apparent lead effect. Many argue, on good grounds, that blood lead elevations are serving as a marker for social disadvantage ie. that they are highly correlated. If so, then the I.Q. deficits could be due to social disadvantage and not lead. They further argue that if the child's social environment could be more accurately measured then the apparent association between lead and I.Q. would disappear completely. Others have raised the equally valid concern that the inclusion of numerous highly inter-correlated social factors into the regression analyses can result in statistical over control and in an under estimate of the true size of lead's effect. This debate can not be resolved through interpretation of the published papers. What can be concluded at the present time from existing published studies is as follows:

1. There are no substantial data yet available that support the contention that low level lead exposure is causally associated with behavioral disorders such as hyperactivity or attention disorders. Further studies with measurement techniques other than questionnaires are needed.

2. There is good evidence for a positive association between level of lead burden and degree of social disadvantage.

3. Prior to statistical adjustment for social covariates, there is a negative association between lead burden and I.Q.

4. After statistical adjustment for social factors have been incorporated into the analyses, the lead: I.Q. relationship is substatially reduced and is usually not statistically significant.

5. If there is a causal association between low level lead burden and I.Q., it is quite small. The shared variance between lead burden and I.Q. is about 5% and the size of the lead effect on group I.Q. is about 2.5 I.Q. points. This is very small relative to other factors known to influence I.Q.

6. If a causal link exists it is most likely to be observed among socially disadvantaged children, where the lead effect interacts with other develomental adversities.

7. There is as yet, no strong evidence that low level lead exposure constitutes a universal hazard to all children.

Further resolution of this issue awaits new cross-sectional studies which incorporate further refinements in methods of behavioral assessment. To this end, the World Health Organization is coordinating the execution of five new cross-sectional studies throughout Europe (Farkas et al., 1984). This coordinating effort is under the direction of Dr. Gerhard Winneke of the University of Dusseldorf. The groups are utilizing a common research protocol. Results

will be forthcoming in 1986. The levels of lead exposure being observed in these studies are likely to be more comparable to those encountered in Canada today than those reported in U.S. studies during the late 1970's.

1979 - Present: Longitudinal Studies

Recognizing the limitations and interpretative difficulities of cross-sectional, retrospective studies, several research groups have undertaken prospective, longitudinal studies. Preliminary, interim reports are now appearing in the literature or being reported at scientific meetings. The research protocols and discription of cohorts being followed have been reported (Bornschein, 1981; Bornschein and Rabinowitz, 1985).

A brief synopsis of early, interim results follows:

Boston Study: This longitudial study of 249 infants has yielded results suggestive of an effect (not always negative) of prenatal lead burden on the incidence of minor physical anomalies and other indices of morbidity. They also report a negative association between lead burden and 12 month Bayley MDI scores. No association between post-natal lead burden and Bayley MDI Scores has been reported (Bellinger et al., 1984).

Cincinnati Study: These investigators are studying a cohort of over 300 children. The cohort is subjected to a wide range of lead exposure levels and experiences a range of social adversities. An interim analysis finds a significant negative association between prenatal PbB and duration

of gestation, as well as birthweight after controlling for appropriate covariates including duration of gestation. A negative association between indices of prenatal lead exposure and Bayley mental and motor scales at 6 months of age has been observed. No effect of postnatal indices of exposure are related to 6 months Bayley scales after controlling for prenatal exposure (Dietrich et al., 1985). In fact early post-natal lead exposure appears to be positively associated with and perhaps due to rapid motor development (Dietrich et al., 1985).

Cleveland Study: Preliminary results on about 150 infants suggests a negative association between cord blood levels and neonatal neurological status. However no direct association between cord PbB and later Bayley MDI scores at 24 months was apparent.

Glasgow Study: This study involves the longitudinal follow-up of 150 infants of mothers exposed to various levels of lead in drinking water during pregnancy. They found lower birthweight with increasing maternal PbB and an increase in length at birth. Performance on the Bayley mental and motor tests at 12 months was associated with birthweight, father's social class and home environment, but <u>not</u> postnatal lead exposure.

Port Pirie Study: These investigators have followed the outcome of over 800 pregnancies in a community surrounding the world's

largest lead smelter. They report a significant positive association between lead burden and preterm delivery which remained statistically significant when a variety of other potentially confounding variables were taken into account. They also report a negative association between Bayley mental developmental index (MDI) scores at 24 months and several indices of postnatal lead burden. This effect remained after controlling for several covariates and confounders, but prenatal lead burden was not controlled.

The longitudinal studies appear to be finding an effect of in utero lead exposure on birthweight and very early performance measures. Conversely these studies have not yet demonstrated any effects of post-natal lead exposure. The long term consequences of these exposures await maturation of these cohorts.

Electrophysiological Studies

In addition to behavioral and cognitive assessments in children, there are a limited number of studies which have examined the association between lead exposure and CNS function as indexed by electrophysiogical changes (Otto et al., 1982; Winneke et al., 1984). These early studies which proport to demonstrate lead neurotoxicity at very low levels of exposure have repeated many of the same errors pointed out previously fo the early cross-sectional retrospective behavioral studies. Absolutely no conclusions can be reached regarding the effects of lead on the electrophysiology of the central nervous system. Drs. Otto, Winneke and others do have new studies about to be initiated which should result in interpretable findings.

Consequences of Early Neurotoxic Insult

If one assumes that fetal and/or infant lead exposure results in a measurable, reproducible deficit in performance on tests such as the Bayley Scales, what can be said of the long term consequences with regard to school performance and other indices of social and academic competency? Obviously, cross-sectional studies, with assessments administered at a single point during the course of development, can not answer such a question. The current longitudinal lead studies will ultimately address this issue, however, these cohorts are still of pre-school age. It is possible however to gain insight into the range of possible outcomes by viewing the results of other longitudinal studies of early CNS insult. Neurotoxins are often viewed as having a deleterious effect on development regardless of the constitutional vulnerability or robustness of the child or the quality of the home environment in which the child develops. While this is undoubtedly true under conditions of very high exposure, it is less likely to be the case at lower levels of exposure. Recent research in the field of fetal malnutrition has demonstrated the inaccuracy and inadequacy of such a concept (Zeskind and Ramey, 1978) (see Table 2). Their study consisted of the random assignment of fetally malnurished (low pondral index) and control infants drawn from a low S.E.S., black population, to environments differing in quality of support for intellectual development. They found that the detrimental effects of fetal malnutrition persisted and became progressively worse in 36 month old infants reared in a nonsupportive environment (General Cognitive Index = 71 $\pm$ 10). Those high risk infants receiving additional stimulation exhibited intellectual performance (96 $\pm$ 11) considerably above those not receiving environmental intervention (71 $\pm$ 10) and performed at a level comparable to those infants not at risk and receiving additional stimu-

lation (98 $\pm$ 14). Thus, the developmental trajectory of infants subjected to various environmental insults is not determined solely by the nature of the insult. It is subject to modification by the child's subsequent interactions with his/her environment. Contrary to the belief of some, a child's cognitive ability as reflected in performance on I.Q. tests is not a static biologic entity, but rather, it is highly labile and subject to the quality of rearing enviornment. Thus it is highly likely that the outcome of any lead insult incurred during infancy will be shaped by the child's social environment, thereby producing a wide spectrum of performance by the time the child reaches school age.

Air Quality Criteria Document, 1984. Appendix 12-C: Independent Peer Review of Selected Studies Concerning Neurobheavioral Effects of Lead Exposure in Nominally Asymptomatic Children.

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TABLE 2

Influence of Fetal Malnutrition and Caregiving Environment on Intellectual Development of Infants

Pondral Index[a]	Infant Stimulation	Age 3 Mo.[c]	Age 18 Mo.[c]	Age 36 Mo.[d]
Average	Yes[b]	102	107	98 ± 14
	No	97	93	84 ± 10
Low	Yes	92	104	96 ± 11
	No	91	86	71 ± 10

(from Zeskind and Ramey, 1981)

[a]ratio of weight to height at birth; used as an index of fetal nutrition

[b]daily participation in a daycare infant stimulation program

[c]Bayley Mental Developmental Index Scores

[d]McCarthy General Cognitive Index Scores (Normal = 100 ± 15)